WT1 gene

Wilms tumor 1

Normal Function

The *WT1* gene provides instructions for making a protein that is necessary for the development of the kidneys and gonads (ovaries in females and testes in males). Within these tissues, the WT1 protein plays a role in cell growth, the process by which cells mature to perform specific functions (cell differentiation), and the self-destruction of cells (apoptosis). To carry out these functions, the WT1 protein regulates the activity of other genes by attaching (binding) to specific regions of DNA. On the basis of this action, the WT1 protein is called a transcription factor.

Health Conditions Related to Genetic Changes

congenital nephrotic syndrome

cytogenetically normal acute myeloid leukemia

Denys-Drash syndrome

At least 80 mutations in the *WT1* gene have been found to cause Denys-Drash syndrome, a condition that affects development of the kidneys and genitalia and most often affects males. These mutations almost always occur in areas of the gene known as exon 8 and exon 9. Most mutations change single protein building blocks (amino acids) in the WT1 protein. The most common mutation that causes Denys-Drash syndrome (found in about 40 percent of cases) replaces the amino acid arginine with the amino acid tryptophan at protein position 394 (written Arg349Trp or R349W).

The mutations that cause Denys-Drash syndrome lead to the production of an abnormal WT1 protein that cannot bind to DNA. As a result, the activity of certain genes is unregulated, which impairs development of the kidneys and genitalia. Abnormal development of these organs leads to the signs and symptoms of Denys-Drash syndrome.

Rarely, a mutation in exon 8 or exon 9 of the *WT1* gene causes a related condition called Frasier syndrome (described below). Because these two conditions share a genetic cause and have overlapping features, some researchers have suggested that these two conditions are part of a spectrum and not two distinct conditions.

Frasier syndrome

At least seven mutations in the *WT1* gene have been found to cause Frasier syndrome, a condition that affects development of the kidneys and genitalia and most often affects males. These mutations almost always occur in an area of the gene known as intron 9. The most common mutation that causes Frasier syndrome (found in over half of affected individuals) changes a single DNA building block (nucleotide) in the *WT1* gene, written as IVS+4C>T. This mutation and others that cause Frasier syndrome alter the way the gene's instructions are pieced together to produce the protein.

The *WT1* gene mutations that cause Frasier syndrome lead to the production of a protein with an impaired ability to control gene activity and regulate the development of the kidneys and reproductive organs, resulting in the signs and symptoms of Frasier syndrome.

Rarely, a mutation in intron 9 of the *WT1* gene causes a related condition called Denys-Drash syndrome (described above). Because these two conditions share a genetic cause and have overlapping features, some researchers have suggested that these two conditions are part of a spectrum and not two distinct conditions.

prostate cancer

WAGR syndrome

The *WT1* gene is located in a region of chromosome 11 that is often deleted in people with WAGR syndrome, which is a disorder that affects many body systems and is named for its main features: a childhood kidney cancer known as Wilms tumor, an eye problem called anirida, genitourinary anomalies, and intellectual disability (formerly referred to as mental retardation). As a result of this deletion, affected individuals are missing one copy of the *WT1* gene in each cell. The loss of this gene is responsible for the genitourinary abnormalities and the increased risk of Wilms tumor in affected individuals.

cancers

Mutations in the *WT1* gene can cause Wilms tumor, a rare form of kidney cancer that usually occurs in early childhood. Some people with Wilms tumor have a mutation in one copy of the *WT1* gene in every cell. Most of these are new mutations that occur during the formation of reproductive cells (eggs and sperm) or in early fetal development, although some may be inherited from a parent. In other people with Wilms tumor, *WT1* gene mutations are present only in the tumor cells. These changes are typically somatic, which means they are acquired during a person's lifetime. *WT1* gene mutations, whether they are somatic or present in every cell, account for 10 to 20 percent of cases of Wilms tumor.

Changes in the activity (expression) of the *WT1* gene are associated with several other forms of cancer. In particular, the *WT1* gene is abnormally expressed in certain types of lung, prostate, breast, and ovarian cancer. Abnormal expression of the *WT1* gene also occurs in some cancers of blood-forming cells (leukemias), such as acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and childhood acute myeloid leukemia (AML). It is unclear what role the WT1 protein plays in the development or progression of cancer.

other disorders

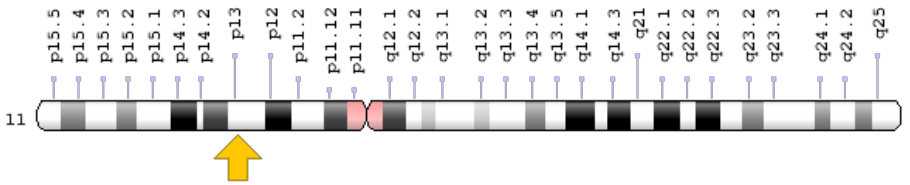
At least two mutations in the *WT1* gene have been found to cause Meacham syndrome. This condition is characterized by abnormalities in the development of the male genitalia, heart, and diaphragm. Individuals with this condition have a typical male chromosome pattern (46,XY) but have external genitalia that do not look clearly male or clearly female (ambiguous genitalia) or have genitalia that appear completely female. Additionally, the internal reproductive organs are female, but they do not develop normally. Individuals with Meacham syndrome typically have heart defects that are present from birth and can vary in severity. They also have a hole in the muscle that separates the abdomen from the chest cavity (the diaphragm), which is called a congenital diaphragmatic hernia. Meacham syndrome is typically fatal in infancy. Approximately a dozen individuals have been described as affected with Meacham syndrome.

Mutations in the *WT1* gene can also cause a condition called isolated nephrotic syndrome. This condition is characterized by an inability of the kidneys to filter waste products from blood, which leads to protein in the urine, swelling (edema), and ultimately, kidney failure. Isolated nephrotic syndrome includes diffuse glomerulosclerosis, in which scar tissue forms throughout the clusters of tiny blood vessels (glomeruli) in the kidneys, and focal segmental glomerulosclerosis, in which glomeruli in only certain areas of the kidneys experience scarring. Mutations in the *WT1* gene most often cause diffuse glomerulosclerosis.

Chromosomal Location

Cytogenetic Location: 11p13, which is the short (p) arm of chromosome 11 at position 13

Molecular Location: base pairs 32,387,775 to 32,435,535 on chromosome 11 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- WIT-2
- WT1_HUMAN
- WT33

Additional Information & Resources

Educational Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology: Wilms tumor http://atlasgeneticsoncology.org/Tumors/WilmsID5034.html
- Cancer Genetics Web http://www.cancerindex.org/geneweb/WT1.htm
- Cancer Medicine (sixth edition, 2003): WT1 gene https://www.ncbi.nlm.nih.gov/books/NBK12914/

GeneReviews

- Wilms Tumor Predisposition https://www.ncbi.nlm.nih.gov/books/NBK1294

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28WT1%5BTI%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- WILMS TUMOR 1
  http://omim.org/entry/194070
- WT1 GENE
  http://omim.org/entry/607102

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/WT1ID78.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=WT1%5Bgene%5D
- HGNC Gene Family: Zinc fingers C2H2-type
  http://www.genenames.org/cgi-bin/genefamilies/set/28
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=12796
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/7490
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